ORIGINAL ARTICLE

Beta-Blockers after Myocardial Infarction and Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Most trials that have shown a benefit of beta-blocker treatment after myocardial infarction included patients with large myocardial infarctions and were conducted in an era before modern biomarker-based diagnosis of myocardial infarction and treatment with percutaneous coronary intervention, antithrombotic agents, high-intensity statins, and renin–angiotensin–aldosterone system antagonists.

METHODS

In a parallel-group, open-label trial performed at 45 centers in Sweden, Estonia, and New Zealand, we randomly assigned patients with an acute myocardial infarction who had undergone coronary angiography and had a left ventricular ejection fraction of at least 50% to receive either long-term treatment with a beta-blocker (metoprolol or bisoprolol) or no beta-blocker treatment. The primary end point was a composite of death from any cause or new myocardial infarction.

RESULTS

From September 2017 through May 2023, a total of 5020 patients were enrolled (95.4% of whom were from Sweden). The median follow-up was 3.5 years (interquartile range, 2.2 to 4.7). A primary end-point event occurred in 199 of 2508 patients (7.9%) in the beta-blocker group and in 208 of 2512 patients (8.3%) in the no–beta-blocker group (hazard ratio, 0.96; 95% confidence interval, 0.79 to 1.16; P=0.64). Beta-blocker treatment did not appear to lead to a lower cumulative incidence of the secondary end points (death from any cause, 3.9% in the beta-blocker group and 4.1% in the no–beta-blocker group; death from cardiovascular causes, 1.5% and 1.3%, respectively; myocardial infarction, 4.5% and 4.7%; hospitalization for atrial fibrillation, 1.1% and 1.4%; and hospitalization for heart failure, 0.8% and 0.9%). With regard to safety end points, hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or implantation of a pacemaker occurred in 3.4% of the patients in the beta-blocker group and in 3.2% of those in the no–beta-blocker group; hospitalization for asthma or chronic obstructive pulmonary disease in 0.6% and 0.6%, respectively; and hospitalization for stroke in 1.4% and 1.8%.

CONCLUSIONS

Among patients with acute myocardial infarction who underwent early coronary angiography and had a preserved left ventricular ejection fraction (≥50%), long-term beta-blocker treatment did not lead to a lower risk of the composite primary end point of death from any cause or new myocardial infarction than no beta-blocker use. (Funded by the Swedish Research Council and others; REDUCE-AMI ClinicalTrials.gov number, NCT03278509.)

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*A list of the REDUCE-AMI investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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The efficacy of beta-blockers in patients with heart failure and reduced ejection fraction is well documented. Trials have also shown that long-term beta-blocker therapy after myocardial infarction reduces mortality by approximately 20%.[1-3] However, these results are from trials that mainly involved patients with large myocardial infarctions and left ventricular systolic dysfunction and were conducted primarily in the 1980s. This era predates advancements such as high-sensitivity cardiac troponins, percutaneous coronary interventions, antithrombotic agents, high-intensity statins, and renin–angiotensin–aldosterone system antagonists. A meta-analysis suggested that in the era of modern reperfusion strategies, beta-blockers did not significantly reduce mortality.[4] Data on the effect of long-term beta-blocker therapy in patients with acute myocardial infarction and preserved ejection fraction are lacking from contemporary, sufficiently powered, randomized clinical trials.

Divergent conclusions have emerged from extensive observational studies and meta-analyses of such studies.[5-10] A Cochrane review underscored the need for new trials in this patient population to address current clinical practices.[11] Despite the lack of clear evidence of benefit in the contemporary setting, current guidelines widely recommend beta-blocker use after myocardial infarction.[12-14] We conducted a trial (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction [REDUCE-AMI]) to investigate whether long-term oral beta-blocker treatment in patients with acute myocardial infarction and preserved left ventricular ejection fraction would lead to a lower risk of a composite end point of death of any cause or new myocardial infarction than no beta-blocker use.

Methods

Trial Design and Oversight

We conducted this registry-based, prospective, open-label, parallel-group, randomized clinical trial in three countries: Sweden (38 centers), Estonia (1 center), and New Zealand (6 centers). The design and rationale of the trial have been published previously.[15] The trial was overseen by a data and safety monitoring board, which performed two interim analyses of patient safety. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). Details about the trial organization and the process of writing the manuscript, as well as a list of participating centers and investigators, are provided in the Supplementary Appendix (available at NEJM.org).

Patients

Adult patients who provided written informed consent 1 to 7 days after myocardial infarction and who had undergone coronary angiography and echocardiography with a preserved left ventricular ejection fraction (≥50%) were eligible. Patients were also required to have obstructive coronary artery disease as documented by coronary angiography (i.e., stenosis of ≥50%, a fractional flow reserve of ≤0.80, or an instantaneous wave-free ratio of ≤0.89 in any segment) at any time point before randomization. Major exclusion criteria were an indication for or contraindication to beta-blocker treatment. To ensure completeness of follow-up, nonresidents of the three trial countries could not undergo randomization. A list of the inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix.

A Quick Take is available at NEJM.org

Trial Treatments and Procedures

Randomization was stratified according to trial center and was performed in a 1:1 ratio with the use of permuted blocks; trial groups were assigned by means of a Web-based system. Patients who were randomly assigned to the beta-blocker group were administered metoprolol (first choice) or bisoprolol (alternative) during the remaining hospital stay and received a prescription for continued use after discharge. The treating physician was encouraged to aim for a dose of at least 100 mg daily for metoprolol and at least 5 mg daily for bisoprolol. Patients were encouraged to continue the use of beta-blockers after discharge until the occurrence of a contraindication. Patients who were randomly assigned to the no–beta-blocker group were discouraged from using beta-blockers as long as there was no other indication than secondary prevention after myocardial infarction.

For blood-pressure control, drugs other than beta-blockers were recommended according to guidelines. If a patient was already receiving treatment with a beta-blocker when enrolled and

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randomly assigned to the no–beta-blocker group, a tapering of the beta-blocker had to be carried out during a period of 2 to 4 weeks. The importance of continuation of the assigned regimen (beta-blockers or no beta-blockers) was documented in patients' health records. Patients received written information explaining the importance of continuing the assigned regimen unless contraindications to beta-blockers or indications for beta-blockers other than for secondary prevention arose. The patient also received a summary of this information in an identification card–size format to wear in case of medical contact.

CLINICAL END POINTS

The primary end point was a composite of death from any cause or new myocardial infarction. Secondary end points were death from any cause, death from cardiovascular causes, myocardial infarction, hospitalization for atrial fibrillation (as a primary diagnosis), and hospitalization for heart failure (as a primary diagnosis). Safety end points were hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or implantation of a pacemaker; hospitalization for asthma or chronic obstructive pulmonary disease (as a primary diagnosis); and hospitalization for stroke. Angina pectoris (according to Canadian Cardiovascular Society class) and dyspnea (according to New York Heart Association class) after 6 to 10 weeks and after 11 to 13 months were also end points.

Details regarding the trial end points are provided in Table S2. The end points of angina pectoris and dyspnea were registered only in Sweden for patients who attended the follow-up visits of the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. The age limit for follow-up visits was below 75 years until 2018 and below 80 years thereafter.

DATA SOURCES

In Sweden, baseline data were collected from the trial randomization module and from the SWEDEHEART registry. The registry is described in detail in the Supplementary Appendix and in a previous article.[16] Information on the date of death or emigration was obtained from the Swedish population registry. Data on a new myocardial infarction during the initial hospital stay and on readmission due to a myocardial infarction were collected from the SWEDEHEART registry. To ensure the correctness of the follow-up data, the principal investigator at each center also validated all myocardial infarctions that were identified by the registry, according to a checklist.

Data on death from cardiovascular causes were obtained from the national cause-of-death registry. Data on atrial fibrillation and heart failure were obtained from the national patient registry, which is a mandatory registry that includes all International Classification of Diseases codes for all hospital admissions in Sweden. Linkage with the national cause-of-death registry and the patient registry was performed at the end of follow up.

Symptoms, including angina and dyspnea, that occurred after 6 to 10 weeks and after 11 to 13 months were registered in SWEDEHEART registry for patients who attended the registry follow-up visits. Data on safety end points (hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or implantation of pacemaker; hospitalization for asthma or chronic obstructive pulmonary disease; and hospitalization for stroke) were obtained from the national patient registry. In Estonia and New Zealand, baseline data were manually entered into an electronic case-report form that had the same structure as the information in the SWEDEHEART registry, and follow-up was performed with the use of health records obtained from the hospital that provided care for the patient.

STATISTICAL ANALYSIS

Before the initiation of the trial, we assumed that the event rate of death from any cause or new myocardial infarction (primary end point) would be 7.2% per year in the no–beta-blocker group. A 16.7% lower risk in the beta-blocker group, corresponding to a 1.2 percentage-point lower absolute risk per year, was considered to be a minimal important difference to detect. During the trial, the total blinded event counts indicated an actual event rate of 3% per year. The sponsor together with the steering committee and patient representatives concluded that a 25% lower risk (corresponding to a 0.9-percentage-point lower absolute risk) would still be a clinically relevant

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effect to detect, so this change was made in the protocol in July 2021. To detect a hazard ratio of 0.75, with 80% power at a two-sided significance level of 5%, we calculated that 379 primary end-point events would be required, which we expected to occur with the enrollment of approximately 5000 patients.

The intention-to-treat analyses included all the patients who were enrolled and underwent randomization. These analyses were based on events that occurred during all follow-up time in each patient from randomization to the end of follow-up. Results regarding all the end points (except symptoms) are presented as cumulative incidence plots and frequency tables, according to randomized trial group, and were analyzed with the use of Cox unadjusted proportional-hazards regression. To account for the competing risk of death from noncardiovascular causes in the analysis of death from cardiovascular causes and for the competing risk of death before outcome for all the end points except the primary composite end point and the secondary end point of death from any cause, we estimated cause-specific hazard ratios for these end points. Proportionality of hazards was assessed by means of visual inspection and analyses with censoring of data after different cutoff points, and post hoc analyses of differences in the restricted mean survival time before the maximum observed follow-up time were presented in case of possible violations. Patients who withdrew from follow-up or who emigrated had their data censored on the day of withdrawal or emigration.

Results for secondary end points are presented, without formal adjustment for multiplicity, to support the understanding of the primary result. The widths of the 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive treatment effects. To estimate a more patient-specific hazard ratio and to investigate model dependence, sensitivity analyses were performed with adjustment for country and for age (as a restricted cubic spline), the presence or absence of diabetes mellitus, and the presence or absence of previous myocardial infarction. To explore possible heterogeneity in the treatment effect, we performed prespecified subgroup analyses of the composite primary end point and the secondary end point of death from any cause. Canadian Cardiovascular Society and New York Heart Association classes were analyzed with the use of proportional-odds logistic regression. Details regarding the statistical analyses, including sensitivity analyses for missing data, are provided in the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From the start of the trial in September 2017 to the end of enrollment in May 2023, a total of 5020 patients underwent randomization, with 4788 patients (95.4%) in Sweden, 32 (0.6%) in Estonia, and 200 (4.0%) in New Zealand (Fig. S1). The characteristics of the patients at baseline were well balanced between the trial groups (Table 1). (Information about missing data is provided in Tables S3 and S4.)

The median age of the patients was 65 years, 22.5% of the patients were women, and 35.2% had an ST-segment elevation myocardial infarction. Regarding risk factors, 46.2% of the patients had hypertension, 14.0% had diabetes mellitus, 7.1% had previously had a myocardial infarction, and 0.7% had previously had heart failure. At the time of hospital admission, 11.6% of the patients were receiving beta-blockers. Coronary angiography revealed one-vessel disease in 55.4% of the patients, two-vessel disease in 27.0%, and left main or three-vessel disease in 16.6%. Percutaneous coronary intervention was performed in 95.5% of the patients, and coronary-artery bypass grafting in 3.9%. At discharge, 97.4% of the patients were receiving aspirin, 95.8% a P2Y12 receptor blocker, 80.2% an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker, and 98.5% a statin.

FOLLOW-UP AND TREATMENT ADHERENCE

Patients were followed until November 16, 2023. Four patients withdrew consent, and 8 emigrated. Of the 4788 patients in Sweden, 4388 (91.6%) were invited to the SWEDEHEART registry follow-up visits; 3836 of these patients (87.4%) attended a follow-up visit in the period from 6 to 10 weeks and 3720 (84.8%) attended a visit in the period from 11 to 13 months.

Of the 2508 patients who had been assigned to the beta-blocker group, 1560 (62.2%) were treated with metoprolol and 948 (37.8%) with bisoprolol. For metoprolol, the median starting

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Table 1. Characteristics of the Patients.*

Characteristic	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)
Median age (IQR) — yr	65 (57–73)	65 (57–73)
Female sex — no. (%)	563 (22.4)	568 (22.6)
Country — no. (%)		
Sweden	2392 (95.4)	2396 (95.4)
Estonia	16 (0.6)	16 (0.6)
New Zealand	100 (4.0)	100 (4.0)
Risk factors — no./total no. (%)		
Current smoking	478/2466 (19.4)	530/2483 (21.3)
Hypertension	1155/2507 (46.1)	1163/2509 (46.4)
Diabetes mellitus	346/2506 (13.8)	354/2509 (14.1)
Previous cardiovascular disease — no./total no. (%)		
Previous myocardial infarction	165/2503 (6.6)	192/2507 (7.7)
Previous PCI	147/2504 (5.9)	175/2505 (7.0)
Previous CABG	33/2504 (1.3)	36/2507 (1.4)
Previous stroke	52/2506 (2.1)	67/2507 (2.7)
Previous heart failure	13/2486 (0.5)	22/2481 (0.9)
Characteristic at presentation		
Chest pain as main symptom — no./total no. (%)	2421/2507 (96.6)	2417/2512 (96.2)
CPR before hospital arrival — no./total no. (%)	10/2483 (0.4)	11/2485 (0.4)
Pulmonary rales — no./total no. (%)	29/2445 (1.2)	42/2462 (1.7)
Median heart rate (IQR) — beats/min†	74 (65–85)	73 (64–84)
Median systolic blood pressure (IQR) — mm Hg‡	150 (135–170)	151 (136–170)
Atrial fibrillation — no./total no. (%)	21/2502 (0.8)	23/2504 (0.9)
ST-segment elevation myocardial infarction — no./total no. (%)	877/2507 (35.0)	892/2512 (35.5)
Current oral beta-blocker treatment — no./total no. (%)	269/2468 (10.9)	302/2472 (12.2)
Median no. of days from hospital admission to randomization (IQR)	2 (1–3)	2 (1–3)
In-hospital course — no./total no. (%)		
Coronary angiography		
No stenosis	26/2484 (1.0)	25/2491 (1.0)
One-vessel disease	1378/2484 (55.5)	1378/2491 (55.3)
Two-vessel disease	676/2484 (27.2)	668/2491 (26.8)
Left main or three-vessel disease	404/2484 (16.3)	420/2491 (16.9)
PCI	2387/2491 (95.8)	2376/2496 (95.2)
CABG	92/2491 (3.7)	103/2496 (4.1)

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Table 1. (Continued.)

Characteristic	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)
Medication at discharge — no./total no. (%)		
Aspirin	2450/2507 (97.7)	2440/2512 (97.1)
P2Y12 receptor blocker	2411/2507 (96.2)	2398/2512 (95.5)
Beta-blocker	2399/2505 (95.8)	247/2512 (9.8)
ACE inhibitor or ARB	1985/2507 (79.2)	2040/2512 (81.2)
Statin	2481/2507 (99.0)	2461/2510 (98.0)
Diuretic agent	211/2507 (8.4)	191/2512 (7.6)
Calcium-channel blocker	416/2508 (16.6)	496/2511 (19.8)

* Patients in the beta-blocker group were given metoprolol (first choice) or bisoprolol (alternative). Data on race and ethnic group were not collected. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, CPR cardiopulmonary resuscitation, IQR interquartile range, and PCI percutaneous coronary intervention.
† Data on heart rate were missing for 19 patients in the beta-blocker group and for 17 in the no–beta-blocker group.
‡ Data on systolic blood pressure were missing for 23 patients in the beta-blocker group and for 22 in the no–beta-blocker group.

dose was 50 mg (interquartile range, 25 to 50), and the median target dose was 100 mg (interquartile range, 100 to 100); for bisoprolol, the median starting dose was 2.5 mg (interquartile range, 2.5 to 2.5), and the median target dose was 5.0 mg (interquartile range, 2.5 to 5.0). Among the patients who attended the SWEDEHEART registry follow-up visits and had their data regarding beta-blocker treatment recorded, 1726 of 1906 (90.6%) in the beta-blocker group were still taking beta-blockers after 6 to 10 weeks and 1500 of 1831 (81.9%) were still taking beta-blockers after 11 to 13 months; in the no–beta-blocker group, 217 of 1924 (11.3%) were taking beta-blockers after 6 to 10 weeks and 269 of 1886 (14.3%) were taking beta-blockers after 11 to 13 months.

END POINTS

The median follow-up was 3.5 years (interquartile range, 2.2 to 4.7) in each trial group. Death from any cause or a new myocardial infarction (primary end point) occurred in 199 of 2508 patients (7.9%; annual event rate, 2.4%) in the beta-blocker group and in 208 of 2512 patients (8.3%; annual event rate, 2.5%) in the no–beta-blocker group (hazard ratio, 0.96; 95% confidence interval, 0.79 to 1.16; P=0.64) (Fig. 1A and Table 2). Beta-blocker treatment did not appear to lead to a lower cumulative incidence of the secondary end points of death from any cause, death from cardiovascular causes, myocardial infarction, hospitalization for atrial fibrillation, and hospitalization for heart failure (Fig. 1B and 1C, Table 2, and Figs. S2, S3, and S4).

The incidence of safety end points also appeared to be similar in the two trial groups (Table 2 and Figs. S5, S6, and S7). An indication of nonproportional hazards for the end point of hospitalization for stroke was observed, so a restricted mean survival time analysis was performed. Among the patients who had attended the SWEDEHEART registry follow-up visits, the incidence and severity of symptoms after 6 to 10 weeks and after 11 to 13 months appeared to be similar in the two trial groups (Fig. S8). Adjustment for country and for age, presence or absence of diabetes mellitus, and presence or absence of previous myocardial infarction did not appreciably change the results regarding the primary end point (Table S5). No apparent association between the target dose of beta-blocker treatment and the primary end point was observed (Fig. S9).

SUBGROUP ANALYSES

The results of subgroup analyses suggested similar treatment effects with respect to the composite primary end point and the secondary end

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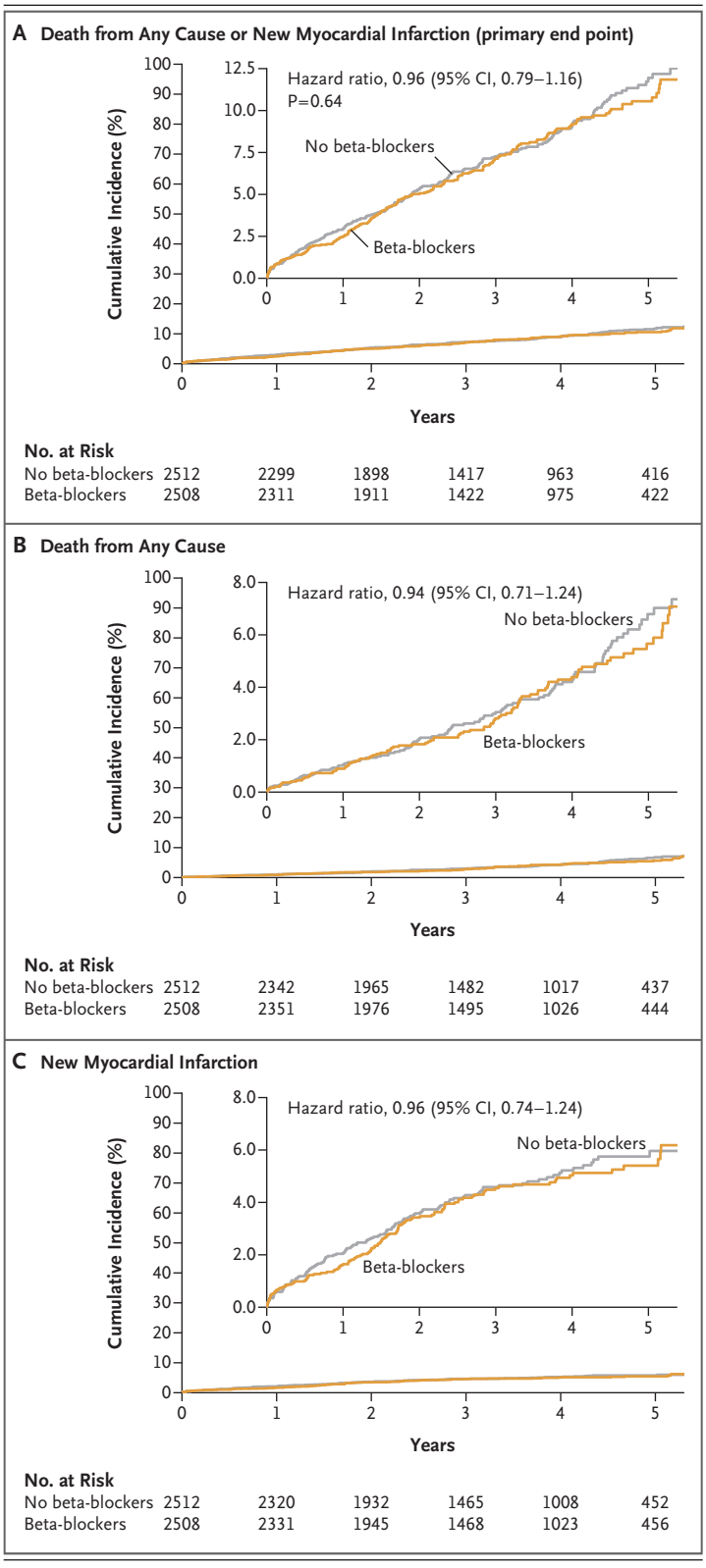
A Death from Any Cause or New Myocardial Infarction (primary end point)
Cumulative Incidence (%)
Hazard ratio, 0.96 (95% CI, 0.79–1.16)
P=0.64
No beta-blockers
Beta-blockers
Years
No. at Risk
No beta-blockers 2512 2299 1898 1417 963 416
Beta-blockers 2508 2311 1911 1422 975 422
B Death from Any Cause
Cumulative Incidence (%)
Hazard ratio, 0.94 (95% CI, 0.71–1.24)
No beta-blockers
Beta-blockers
Years
No. at Risk
No beta-blockers 2512 2342 1965 1482 1017 437
Beta-blockers 2508 2351 1976 1495 1026 444
C New Myocardial Infarction
Cumulative Incidence (%)
Hazard ratio, 0.96 (95% CI, 0.74–1.24)
No beta-blockers
Beta-blockers
Years
No. at Risk
No beta-blockers 2512 2320 1932 1465 1008 452
Beta-blockers 2508 2331 1945 1468 1023 456

Figure 1. Death from Any Cause and New Myocardial Infarction.
The primary end point was a composite of death from any cause or new myocardial infarction. Secondary end points included the individual components of the primary end point. In all panels, the inset shows the same data on an enlarged y axis. CI denotes confidence interval.

point of death from any cause across the prespecified subgroups (Figs. S10 and S11). The exception was the subgroup of patients who were taking a beta-blocker at admission, in which randomization to the beta-blocker group tended to be associated with a higher risk of a primary end-point event.

DISCUSSION

In this registry-based, prospective, randomized, open-label, parallel-group trial conducted across 45 centers, most of which were in Sweden, the early initiation of oral beta-blocker treatment after an acute myocardial infarction in patients with a preserved left ventricular ejection fraction did not lead to a lower cumulative incidence of death from any cause or new myocardial infarction (composite primary end point). In addition, no appreciable between-group differences were observed in the analyses of secondary efficacy and safety end points. After 1 year, the incidence and severity of symptoms appeared to be similar in the two groups among the patients in Sweden who attended registry follow-up visits and had symptoms assessed. The absence of an effect of beta-blocker treatment on the cumulative incidence of death or myocardial infarction appeared to be consistent across all prespecified subgroups.

The baseline characteristics indicated that the patients who were included in the trial were representative of the population of patients with myocardial infarction and preserved ejection fraction in the trial countries (Table S6) and were generally at low risk for new cardiac events. The patients were well treated with early revascularization procedures and received evidence-based medications at discharge. The overall annual event rates for the primary end point (2.4% in the beta-blocker group and 2.5% in the no–beta-blocker group) were lower than we had expected

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Table 2. Primary and Secondary End Points.*

End Point	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)	Hazard Ratio (95% CI)†	P Value
	number (percent)			
Primary end point				
Death from any cause or myocardial infarction	199 (7.9)	208 (8.3)	0.96 (0.79 to 1.16)	0.64
Secondary end points				
Death from any cause	97 (3.9)	103 (4.1)	0.94 (0.71 to 1.24)	
Death from cardiovascular causes	38 (1.5)	33 (1.3)	1.15 (0.72 to 1.84)	
Myocardial infarction	112 (4.5)	117 (4.7)	0.96 (0.74 to 1.24)	
Hospitalization for atrial fibrillation	27 (1.1)	34 (1.4)	0.79 (0.48 to 1.31)	
Hospitalization for heart failure	20 (0.8)	22 (0.9)	0.91 (0.50 to 1.66)	
Safety end points				
Hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or implantation of a pacemaker	86 (3.4)	80 (3.2)	1.08 (0.79 to 1.46)	
Hospitalization for asthma or COPD	15 (0.6)	16 (0.6)	0.94 (0.46 to 1.89)	
Hospitalization for stroke	36 (1.4)	46 (1.8)	6.80 (−7.11 to 20.72)†	

* For all end points except the composite primary end point and the secondary end point of death from any cause, death before an event is a competing risk, and the analysis shows cause-specific hazards. See the detailed statistical methods in the Supplementary Appendix. CI denotes confidence interval, and COPD chronic obstructive pulmonary disease.

† For the safety end point of hospitalization for stroke, the table shows the difference in the restricted mean survival time in days within the largest follow-up time (2224 days), which was a post hoc analysis. Within the largest follow-up time, the restricted mean survival time was 2195 days in the beta-blocker group and 2188 days in the no–beta-blocker group.

before the initiation of the trial. We designed the trial as a superiority trial, powered to detect a 25% lower risk of death or myocardial infarction with beta-blocker treatment (corresponding to a 0.7-percentage-point lower risk per year, given the actual annual event rates that we observed), which we regarded as a clinically relevant effect. Although the neutral result that we found in this trial does not rule out either a small beneficial or detrimental effect, the overlapping time-to-event curves that were observed throughout the follow-up period and the consistent results in all the prespecified subgroups and for the secondary end points make a clinically relevant difference unlikely. Our findings are also consistent with the results of several large observational studies and meta-analyses of such studies.[5,7,9,10] The possible signal of a harmful effect of beta-blocker treatment in the subgroup of patients who were taking a beta-blocker at admission is of unclear relevance and is probably a spurious finding.

Our trial included only patients who had a left ventricular ejection fraction of at least 50%. During the planning phase, many potential investigators were hesitant to include patients who had a mid-range left ventricular ejection fraction (40 to 49%). We also wanted to keep the trial population as homogeneous as possible, since any interaction between trial group and a subgroup makes the trial results more difficult to interpret and generalize. A later meta-analysis of clinical trials involving patients with a mid-range left ventricular ejection fraction suggested a beneficial effect of beta-blockers generally, and a large Korean registry suggested a benefit specifically after myocardial infarction.[7,17]

We allowed only beta-1–receptor selective blockers (metoprolol and bisoprolol) because these drugs had the best documentation for long-term treatment and had been used extensively in the countries involved in the trial. Indications for beta-blockers other than secondary prevention was an exclusion criterion. We also

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mandated an early invasive strategy because it reflects a contemporary treatment strategy — that is, the basis for reevaluation of beta-blockers in a new trial. Three other large, ongoing trials examining long-term treatment with beta-blockers in patients with myocardial infarction and preserved fraction have defined a preserved ejection fraction of at least 40% and also are allowing the use of nonselective beta-blockers.[18-20] Two of the trials also include patients being treated without an early invasive approach.[18,19]

The doses of beta-blockers that were used in our trial were lower than those in previous trials. However, the doses that were used in our trial mirror the current practice of beta-blocker treatment, and no apparent association between the planned target dose of beta-blocker treatment and the primary end point was observed. Results from contemporary observational studies comparing various doses of beta-blockers have not shown any clear association with outcome.[21,22] A study from the SWEDEHEART registry that compared 33,126 patients who received a prescription for at least 50% of the target beta-blocker dose at discharge with 64,449 patients who received a prescription for less than 50% of that dose did not show a between-group difference in outcome.[22]

Our trial has several limitations. First, it was an open-label trial, because blinding was not judged to be feasible. Data on clinical end points were obtained from the SWEDEHEART registry and the Swedish Population Registry and were not centrally adjudicated. However, this approach should have had a limited effect on the hard composite primary end point, whereas results regarding softer end points such as symptoms need to be interpreted more cautiously. During follow-up, investigators reviewed electronic health records to confirm that reported new myocardial infarctions in the SWEDEHEART registry fulfilled the criteria for a myocardial infarction according to the treating physician, and any misclassification should have been equally distributed over the two randomized trial groups.

Second, only safety end points that are associated with hospitalization were assessed. Third, a limitation of pragmatic trials of routinely used therapy is the potential for crossovers. Despite strategies to mitigate this issue, among patients with available information, 14% of those who had been assigned to the no–beta-blocker group were taking beta-blockers after 1 year of follow-up, and we do not yet have information about beta-blocker use after the first year. The adherence to the assigned beta-blocker regimen mirrored patterns that are observed in everyday clinical practice[23,24]; however, we cannot rule out the possibility that the use of beta blockers in the no–beta-blocker group contributed to our null finding.

In this registry-based, prospective, randomized, open-label, parallel-group trial that investigated whether oral beta-blocker therapy that was initiated early in patients with myocardial infarction who underwent early coronary angiography and had a preserved left ventricular ejection fraction would improve long-term outcome, beta-blocker treatment did not result in a lower cumulative incidence of the composite primary end point of death from any cause or new myocardial infarction.

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APPENDIX

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